Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Normopress Tablet 50mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Tablet contains 50 mg of losartan (as potassium salt)
Excipient; lactose

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

White Colored Oval Shaped Film Coated Tablet.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

As with all angiotensin II type 1 receptor (AT1) antagonists, losartan is indicated for the treatment of hypertension. It may also delay progression of diabetic nephropathy and is associated with a positive clinical outcome in that regard. It is a suitable pharmacological agent for the reduction of renal disease progression in patients with type 2 diabetes, hypertension, and microalbuminuria (>30 mg/24 hours) or proteinuria (>900 mg/24 hours).

Although clinical evidence shows calcium channel blockers and thiazide-type diuretics are preferred first-line treatments for most patients (from both efficacy and cost), an angiotensin II receptor antagonist such as losartan is recommended as first-line treatment in patients under the age of 55 who cannot tolerate an ACE inhibitor. The LIFE study demonstrated losartan was significantly superior to atenolol in the primary prevention of adverse cardiovascular events (myocardial infarction or stroke), with a significant reduction in cardiovascular morbidity and mortality for a comparable reduction in blood pressure. A study hints that losartan has a beneficial effect on mitochondria by reversing age related dysfunction in maintaining normal blood pressure and cellular energy usage. The maximal effects on blood pressure usually occur within 3–6 weeks upon starting losartan.

Losartan is also available as hydrochlorothiazide/losartan, a combination drug with a low-dose thiazide diuretic to achieve an additive antihypertensive effect.

4.2 Posology and method of administration

The usual starting dose of Losartan potassium is 50 mg once daily, it can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

Losartan tablets should be swallowed with a glass of water. Losartan may be administered with or without food.

Hypertension

The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily (in the morning). Losartan may be administered with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide)

Pediatric hypertension

There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-16 years old for the treatment of hypertension (see 5.1: Pharmacodynamic properties). Limited pharmacokinetic data are available in hypertensive children above one month of age (see 5.2 : Pharmacokinetic properties).

In patients >50 kg, the usual dose is 50 mg once daily. In exceptional cases the dose can be adjusted to a maximum of 100 mg once daily. Doses above 1.4 mg/ kg (or in excess of 100 mg) daily have not been studied in pediatric patients.

Losartan is not recommended for use in children under 6 years old, as limited data are available in these patient groups. It is not recommended in children with glomerular filtration rate < 30 ml/ min / 1.73 m2 , as no data are available (see also section 4.4).

Losartan is also not recommended in children with hepatic impairment (see also section 4.4).

Hypertensive type II diabetic patients with proteinuria ≥ 0.5 g/day the usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response from one month after initiation of therapy onwards. Losartan may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors)

Heart Failure The usual initial dose of Losartan in patients with heart failure is 12.5 mg once daily. The dose should generally be titrated at weekly intervals (i.e. 12.5 mg daily, 25 mg daily, 50 mg daily) to the usual maintenance dose of 50 mg once daily, as tolerated by the patient.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG The usual starting dose is 50 mg of Losartan once daily. A low dose of hydrochlorothiazide should be added and/ or the dose of Losartan should be increased to 100 mg once daily based on blood pressure response.

Use in patients with intravascular volume depletion: For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see section 4.4).

Use in patients with renal impairment and haemodialysis patients: No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.

Use in patients with hepatic impairment: A lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 4.4).

Use in Elderly Although consideration should be given to initiating therapy with 25 mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly

4.3 Contraindications

Renal Artery Stenosis, Abnormally Low Blood Pressure, Liver Problems, Mild to Moderate Kidney Impairment, Pregnancy, Decreased Blood Volume, High Amount of Potassium in the Blood Special warning and precautions for use.

Losartan should not be taken by patients who are diabetic and taking aliskiren.

Usage in pregnancy and lactation.

Losartan potassium should not be used in pregnancy and lactation.

4.4 Special warnings and precautions for use

Hypersensitivity Angiooedema. Patients with a history of angiooedema (swelling of the face, lips, throat, and/ or tongue) should be closely monitored (See section 4.8)

Hypotension and Electrolyte/Fluid Imbalance Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of Losartan potassium, or a lower starting dose should be used (see section 4.2). This also applies to children.

Electrolyte imbalances Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalemia was higher in the group treated with Losartan as compared to the placebo group (see section 4.8, 'Hypertension and type 2 diabetes with renal disease - Investigations' and 'Post-marketing experience - Investigations' Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a Creatinine Clearance between 30-50 ml/ min should be closely monitored. The concomitant use of potassium sparing diuretics, potassium supplements and potassium containing salt substitutes with losartan is not recommended (see section 4.5).

Liver Function Impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore, losartan must not be administered in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2). Losartan is also not recommended in children with hepatic impairment (see section 4.2).

Renal Function Impairment
As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin angiotensin aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction). As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Use in pediatric patients with renal function impairment Losartan is not recommended in children with glomerular filtration rate < 30ml/ min/ 1.73 m2 as no data are available (see

section 4.2). Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended.

Renal transplantation
There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan tablets is not recommended.

Coronary heart disease and cerebrovascular disease as with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

Heart failure In patients with heart failure, with or without renal impairment, there is - as with other drugs acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment. There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life-threatening cardiac arrhythmias. Therefore, losartan should be used with caution in these patient groups. The combination of losartan with a beta-blocker should be used with caution (see section 5.1).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorbtion
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption should not take this medicine.

Pregnancy
Losartan should not be initiated during pregnancy. Unless continued losartan therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6)

Other warnings and precautions
As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

4.5 Interaction with other medicinal products and other forms of interaction

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

Lithium: As with other drugs which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists (including losartan) may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving losartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including losartan, may be attenuated by NSAIDs, including selective COX-2 inhibitors.

Dual Blockade of the Renin-Angiotensin System (RAS): Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function, and electrolytes in patients on Losartan and other agents that affect the RAS.
Do not co-administer aliskiren with Losartan in patients with diabetes. Avoid use of aliskiren with Losartan in patients with renal impairment (GFR < 60 ml/min).

4.6 Pregnancy and lactation

The drug should not be used in pregnant women and lactating mothers. They are used if the potential benefit outweighs the risk involved.

Pediatric use

The usual recommended starting dose is 0.7 mg/kg once daily (up to 50 mg total) administered as a tablet or a suspension. Dosage should be adjusted according to blood pressure response. Doses above 1.4 mg/kg (or in excess of 100 mg) daily have not been studied in pediatric patients. Losartan is not recommended in pediatric patients less than 6 years of age or in pediatric patients with glomerular filtration rate less than 30 mL/min/1.73 m²

4.7 Effects on the ability to drive and use machines

Not Known

4.8 Undesirable effects

The most common side effects for losartan are upper respiratory infections or stuffy nose, dizziness, and back pain. Patients who are diabetic may also commonly experience diarrhea, fatigue, low blood pressure, low blood sugar, elevated potassium, and chest pain. More serious side effects include low blood pressure and allergic reaction.

In controlled clinical trials for essential hypertension, hypertensive patients with left ventricular hypertrophy, chronic heart failure as well as for hypertension and type 2 diabetes mellitus with renal disease, the most common adverse event was dizziness

4.9 Overdose:

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Neither losartan nor its active metabolite can be removed by hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties:

Losartan:
Pharmaco-therapeutic group: selective, competitive angiotensin II receptor type 1 (AT_1) receptor antagonist
ATC code: C09C A01

Mechanism of action

Losartan is a selective, competitive angiotensin II receptor type 1 (AT_1) receptor antagonist, reducing the end organ responses to angiotensin II. Losartan administration results in a decrease in total peripheral resistance (afterload) and cardiac venous return (preload). All of the physiological effects of angiotensin II, including stimulation of release of aldosterone, are antagonized in the presence of losartan. Reduction in blood pressure occurs independently of the status of the renin-angiotensin system. As a result of losartan dosing, plasma rennin activity increases due to removal of the angiotensin II feedback.

Losartan is a uricosuric. Because it can cause hyperkalemia, potassium supplements or salt substitutes containing potassium should not be used without appropriate monitoring by a physician.

Pharmacodynamic effects

As with all angiotensin II type 1 receptor (AT_1) antagonists, losartan is indicated for the treatment of hypertension. It may also delay progression of diabetic nephropathy and is associated with a positive clinical outcome in that regard. It is a suitable pharmacological agent for the reduction of renal disease progression in patients with type 2 diabetes, hypertension, and microalbuminuria (>30 mg/24 hours) or proteinuria (>900 mg/24 hours).

5.2 Pharmacokinetic properties

Losartan

Absorption: Well absorbed. Food decreases absorption but has only minor effects on losartan AUC or AUC of active metabolite. Systemic bioavailability is about 33%. T_{max} is

1 h (losartan) and 3 to 4 h (metabolite). While C_{max} of drug and active metabolite are equal, metabolite AUC is 4 times greater than that of losartan.

Distribution: Linear pharmacokinetics. Vd is 34 L (losartan) and 12 L (metabolite). Losartan and active metabolite are highly bound to plasma proteins, primarily albumin. Neither losartan or metabolite accumulates in plasma upon repeated daily dosing.

Metabolism: Undergoes substantial first-pass metabolism by CYP-450 2C9 and 3A4 enzymes. Fourteen percent of an oral dose is converted to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonist activity.

Excretion: The t ½ is 2 h (losartan) and 6 to 9 h (metabolite). Renal Cl is 75 mL/min (losartan) and 25 mL/min (metabolite). Total plasma Cl is 600 mL/min (losartan) and 50 mL/min (metabolite). Biliary excretion contributes to the elimination of losartan and metabolite. About 4% is excreted unchanged in the urine and 6% excreted as active metabolite in urine.

Special populations

Renal Function Impairment

Plasma concentrations and AUC of losartan and its active metabolite are increased 50% to 90% and renal Cl reduced 55% to 85% in patients with mild (CrCl 50 to 74 mL/min) and moderate (CrCl 30 to 49 mL/min) renal function impairment. Make dose adjustments as needed unless the patient is volume depleted.

Hepatic Function Impairment

Plasma concentrations of losartan are increased 5 times and active metabolite increased 1.7 times in patients with mild to moderate alcoholic cirrhosis. Total plasma Cl of losartan is reduced about 50% and oral bioavailability is increased 2 times. A lower starting dose is recommended.

Gender

Plasma losartan concentrations are twice as high in hypertensive women as hypertensive men, but plasma concentrations of active metabolite are similar. No dosage adjustment is necessary.

6. PHARMACEUTICAL PARTICULARS:

1. List of excipients

For Core

- ➢ Lactose
- ➢ Sodium Starch Glycolate (Primogel)
- ➢ Povidone K-30
- ➢ Magnesium Stearate
- ➢ Isopropyl Alcohol

For Film coating:

- ➢ Opadry OY-C-7000A (White)
- ➢ Titanium Dioxide
- ➢ Methanol
- ➢ Methylene Chloride
- ➢ Eudragit E-100
- ➢ Isopropyl Alcohol
- ➢ Polyethylene Glycol-6000

2. Incompatibilities
Not applicable.

3. Shelf life
2 years

4. Special precautions for storage
- ➢ Store below 30^{o}C.
- ➢ Protect from heat, sunlight and moisture.
- ➢ Keep away from children.

5. Nature and contents of container.
1 x 10's tablets packed in Alu Alu Blister, in bleach board unit carton with leaflet.

7. Marketing Authorization Holder:
M/s CCL Pharmaceuticals (Pvt.) Ltd.,
65-Industrial Estate, Kot Lakhpat, Lahore,
Pakistan.

8. Marketing Authorization number:
TAN 22 HM 0134

9- Date of Authorization:

April 13, 2022

10- DATE OF REVISION OF THE TEXT:

01-06-2022